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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,446	10/24/2000	Suzana Petanceska	0630/1G184-US1	2608

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EXAMINER
WARE, TODD

ART UNIT	PAPER NUMBER
1615	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/695,446	Applicant(s) PETANCESKA ET AL.
	Examiner Todd D Ware	Art Unit 1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of supplemental information disclosure statement filed 3-19-02, request for extension of time, and amendment both filed 3-22-02 is acknowledged. Claims 8, 16, and 20 have been amended as requested. Claims 1-30 are pending.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3, 5-6, 20-21, and 23-25 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lee et al (WO 98/43647; hereafter '647).

'647 discloses administration of estrogenic compounds (17β-estradiol) to reduce or maintain low levels of amyloid precursor protein (APP) for treatment of Alzheimer's Disease (AD) through reduction in amyloid peptides (abstract; page 7, lines 26-30; page 10, lines 10-14; page 21, line 5 - page22, line 13). '647 also discloses a method for determining the capacity of a drug to inhibit the expression, production, or formation of APP in a cell comprising contacting an estrogenic drug with a cell culture that has the capacity to synthesize APP. The level of APP produced is then compared to a control (page 11, lines 20-29). Since the compositions of '647 and the instant claims appear to be the same and both are related to treatment of AD, it is submitted that the instant

claims are directed to the mechanism of action of '647 and are thus inherent in '647 and the burden is shifted to the applicants to show a difference (MPEP 2112; *EMI Group North America Inc v. Cypress Semiconductor Corp* 60 USPQ2d 1423; *Ex parte Novitski* 26 USPQ2d 1389; *Atlas Powder Co. v. IRECO Inc* 51 USPQ2d 1943).

Response to Arguments

3. Applicant's arguments filed 3-22-02 have been fully considered but they are not persuasive. Applicant argues that '647 only discloses a method of reducing the level of APP in vitro and does not meet the instant limitation requiring in vivo reduction of the level of APP. This argument is not found persuasive. '647 discloses the "object of this invention is to provide compositions and methods for modulating expression, production, or formation of amyloid precursor protein (APP) in a subject comprising administering to the subject an effective amount of a lipophilic hormone, an analog of a lipophilic hormone, a substance that is a ligand, an agonist, or an antagonist of a receptor that is coupled to a lipophilic hormone, and a pharmaceutically acceptable carrier or diluent" (page 6, lines 23-28). It continues on page 13, lines 22-29, that this occurs through administration of a therapeutically effective amount of an active compound such as an analog of estrogen and that this amount will be ultimately decided by the attending physician within the scope of sound medical judgment. Furthermore, '647 discloses on page 14, lines 6-13, that the total daily dose of the active compounds of the present invention are administered to a subject in a single or in divided doses in amounts from about 0.01 to 25 mg/kg body weight or more usually from about 0.1 to 15 mg/kg body weight and that "treatment regimens according to the

present invention comprise administration to a human or other mammal in need of such treatment from about 1 mg to about 1000 mg of the active substances of this invention per day in multiple doses or in a single dose of from 1 mg, 5 mg, 10 mg, 100 mg, 500 mg or 1000 mg." The in vitro experiments applicant refers to are indicative of results that occur in vivo for the reasons disclosed in '647 on page 21, lines 5-22.

4. Claims 1-3, 5-6, 20-21, and 23-25 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lee et al (WO 98/43647; hereafter '647) in combination with Borchelt et al (1996) (see MPEP 2131.01 regarding multiple reference 35 U.S.C. 102 rejections).

'647 is relied upon for all that it teaches previously. Borchelt disclose a role for the ratio of Aβ42 to Aβ20 in the pathogenesis of AD. Accordingly, Borchelt is relied upon for disclosing a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of AD. Therefore, since the compositions of '647 and the instant claims appear to be the same and both are related to treatment of AD, it is submitted that the instant claims are directed to the mechanism of action of '647 and are thus inherent in '647 and the burden is shifted to the applicants to show a difference (MPEP 2112; *EMI Group North America Inc v. Cypress Semiconductor Corp* 60 USPQ2d 1423; *Ex parte Novitski* 26 USPQ2d 1389; *Atlas Powder Co. v. IRECO Inc* 51 USPQ2d 1943).

Response to Arguments

5. Applicant's arguments filed 3-22-02 have been fully considered but they are not persuasive. Applicant argues that Borchelt does not make the missing matter of '647

clear arguing that Borchelt does not show a correlation between APP expression and the ratio of Aβ peptides. However, Borchelt discloses that the processing of APP leads to increased levels of Aβ peptides. Thus, reduction in expression of APP, as disclosed in '647, results in less APP available for post-processing that results in elevated concentrations of Aβ peptides. Therefore, the instant method is inherent within '647.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6, 15, 18-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Lee et al (WO 98/43647; hereafter '647).

'647 discloses administration of estrogenic compounds (17β-estradiol) to reduce or maintain low levels of amyloid precursor protein (APP) for treatment of Alzheimer's Disease (AD) through reduction in amyloid peptides (abstract; page 7, lines 26-30; page 10, lines 10-14; page 21, line 5 - page22, line 13). '647 also discloses a method for determining the capacity of a drug to inhibit the expression, production, or formation of APP in a cell comprising contacting an estrogenic drug with a cell culture that has the capacity to synthesize APP. The level of APP produced is then compared to a control (page 11, lines 20-29). Since the compositions of '647 and the instant claims appear to be the same and both are related to treatment of AD, it is submitted that the instant claims are directed to the mechanism of action of '647 and are thus inherent in '647 and the burden is shifted to the applicants to show a difference (MPEP 2112; *EMI Group North America Inc v. Cypress Semiconductor Corp* 60 USPQ2d 1423; *Ex parte Novitski* 26 USPQ2d 1389; *Atlas Powder Co. v. IRECO Inc* 51 USPQ2d 1943). '647 does not teach use of equine estrogen as the estrogenic compound, however it would have been obvious to one skilled in the art at the time of the invention to use equine estrogen as it would have the same characteristics as non-equine estrogen since the structure is the same. Therefore the burden is shifted to the applicants to demonstrate the criticality of equine estrogen. '647 also does not specifically teach administering the estrogenic compound for at least ten days, however it would have been obvious to one skilled in the art at the time of the invention to administer the compound for at least ten days since '647 shows that administration reduces the probability of onset of AD and that this

would be effective in estrogen deficient postmenopausal women. Thus, administration would occur indefinitely after menopause.

Response to Arguments

9. Applicant's arguments filed 3-22-02 have been fully considered but they are not persuasive. Applicant's argument is similar to that made for the above rejection over '647 under 35 U.S.C. 102. In response, it is again submitted that '647 contemplates in vivo as well as in vitro for the reason stated above in paragraph 3 of the instant Office Action.

10. Claims 1-6, 15, 18-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Lee et al (WO 98/43647; hereafter '647) in view of Borchelt et al (1996).

'647 is relied upon for all that it teaches as stated previously. '647 does not specifically teach a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of AD.

Borchelt is relied upon for disclosing a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of AD.

Accordingly, it would have been obvious to one skilled in the art at the time of the invention to combine '647 and Borchelt to measure the amounts and/or ratio of Aβ42 to Aβ20 to determine whether a compound is effective at reducing these levels or ratio.

Response to Arguments

11. Applicant's arguments filed 3-22-02 have been fully considered but they are not persuasive. Applicant's argument is similar to that made for the above rejection over '647 in combination with Borchelt under 35 U.S.C. 102. In essence, applicant argues

that since neither Borchelt nor '647 teaches a role for the ratio of Aβ42 to Aβ40 in AD, neither reference provides the needed motivation to combine the references. However, Borchelt teaches that the processing of APP leads to increased levels of Aβ peptides. Therefore, it would have been obvious to one skilled in the art at the time of the invention to reduce concentrations of Aβ peptides through reduction in expression of APP to reduce post-processing of APP which results in elevated concentrations of Aβ peptides.

12. Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Lee et al (WO 98/43647; hereafter '647) in combination with Borchelt et al (1996) and further in combination with Simpkins et al (1997). Claims directed to orchidectomy are further rejected in view of Williams and Stancel (Goodman and Gilman's, 1996).

'647 and Borchelt are relied upon for all that they teach as stated previously. Neither teaches orchidectomy or ovariectomy (OVX).

Simpkins is relied upon for teaching OVX as a model for postmenopausal changes.

Accordingly, it would have been obvious to one skilled in the art at the time of the invention to combine '647, Borchelt and Simpkins to utilize OVX as a model for postmenopause and determination of the capacity of a drug to treat AD through measurement of amounts and/or ratio of Aβ42 to Aβ20.

Williams and Stancel is relied upon for teaching synthesis of estradiol from testosterone.

Accordingly, it would have been obvious to one skilled in the art at the time of the invention to utilize orchidectomized animals to study the capacity of a drug to treat AD in males.

Response to Arguments

13. Applicant's arguments filed 3-22-02 have been fully considered but they are not persuasive. Applicant's argument is similar to that made for the above rejection over '647 in combination with Borchelt under 35 U.S.C. 103 further arguing that neither the Simpkins nor the Williams and Stancel references cure the deficiencies of '647 and Borchelt. Therefore the response in paragraph 11 of the instant Office Action is again relied upon. The teachings of Borchelt that the processing of APP leads to increased levels of Aβ peptides renders obviousness to one skilled in the art at the time of the invention to reduce concentrations of Aβ peptides through reduction in expression of APP to reduce post-processing of APP which results in elevated concentrations of Aβ peptides. Combination with Simpkins makes it obvious to utilize OVX as a model for postmenopause and determination of the capacity of a drug to treat AD through measurement of amounts and/or ratio of Aβ42 to Aβ20. Further combination with Williams and Stancel makes it obvious to utilize orchidectomized animals to study the capacity of a drug to treat AD in males.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

tw
June 27, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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